



Multicomponent Reactions

Synthesis of Ugi 4-CR and Passerini 3-CR Adducts under Mechanochemical Activation

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Abstract: The successful application of a mechanochemical activation strategy that employs high-speed ball milling (HSBM) conditions for isocyanide-based multicomponent reactions (IMCRs) was developed. The syntheses of valuable Ugi (by a liquid-assisted grinding process) and Passerini (under solventfree conditions) adducts were achieved by using this method. The protocol disclosed herein allows for the modular synthesis of various compounds according to green chemistry principles, specifically, environmentally friendly conditions, high atom economy, and the absence of toxic byproducts.

Introduction

Green or sustainable chemistry is an important philosophical and practical concept that focuses on the design of cleaner processes to reduce or eliminate the impact of potentially hazardous pollutants on humans and the environment. Anastas and Warner introduced the green chemistry concept in the 1990s, which is based on twelve general principles and represents a remarkable step towards the protection of the environment.^[1] These principles, which are fundamental in organic chemistry, include the minimization or complete removal of solvents in chemical transformations, which is indeed highly desirable from both economic and ecological considerations at small academic laboratories and large industrial plants.^[2] In this regard, interest has increased in recent years for the development of "greener" processes in organic chemistry that use nontraditional energy sources, such as microwave irradiation, ultrasound activation, and more recently high-speed ball-milling techniques through mechanochemical activation.^[3]

In particular, extensive studies of the solid-phase synthesis of different materials as well as the evaluation of grinding protocols (fine pulverization) to prepare active ingredients for industrial applications that employ ball-milling activation have been reported.^[4] Indeed, rapid growth in the use of mechanochemical activation in various areas of organic chemistry such as organocatalysis,^[5] metal-mediated C–C bond formation,^[6] heterocyclic chemistry,^[7] amide and peptide synthesis,^[8] supramolecular chemistry,^[9] polymerizations,^[10] and cycloaddition reactions^[11] has been documented. The salient advantages of a mechanochemically driven reaction include: (a) its

 [a] Departamento de Química, Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, Av. IPN # 2508, San Pedro Zacatenco 07360, México, D. F., México E-mail: ejuarist@cinvestav.mx http://quimica.cinvestav.mx/Directorio/Investigadores/Dr-Eusebio-Juaristi-y-Cosio environmentally friendly nature (minimizing or elimination of solvent use), (b) the typical need of shorter reaction times, (c) its low energy costs, and (d) the use of simple reaction conditions. Despite the attractive well-established features associated with the ball-milling technique, it is still an open area of study in terms of the many unexplored potential applications to modern areas of organic synthesis, such as multicomponent reactions.

In 2008 Chiu et al. reported the one-pot multicomponent construction of [2]rotaxanes by using a mechanochemical activation (MA) approach (Scheme 1, Equation A).^[12] Similarly, Severin, et al. reported the synthesis of several macrocycles in good yields under solvent-free ball-milling conditions (Scheme 1, Equations B and C).^[13] In addition, synthetic approaches to heterocyclic systems such as pyrrole rings have been reported by Menéndez and co-workers (Scheme 1, Equation D).^[14] Other multicomponent reactions (MCRs) activated by high-speed ball milling (HSBM) have afforded various dihydropyrimidones (Scheme 1, Equation F),^[16] and various 4*H*-pyrans (Scheme 1, Equation G).^[17] It is therefore clear that mechanochemical activation of multicomponent reactions is a promising field of research within the area of green chemistry.

Isocyanide-based multicomponent reactions (IMCRs) are an important tool in modern organic synthesis, for example, in the construction of a wide range of heteroatom-containing molecules with increased structural diversity. Diverse libraries of compounds can be obtained by simply varying the starting materials of these reactions.^[18] In this regard, the Ugi 4-CR (four-component reaction) and Passerini 3-CR (three-component reaction) represent two of the most explored transformations in this field, as shown by the large number of publications reported to date.^[19] Interestingly, several studies concerning the solvent-free syntheses of Ugi and Passerini adducts under magnetic stirring,^[20] ultrasound,^[21] microwave-assisted,^[22] and manual grinding^[23] activation have been reported. Nevertheless, the use of mechanochemical activation in IMCRs is still an issue that requires attention.

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Scheme 1. Salient examples of multicomponent reactions carried out under high-speed ball-milling conditions (CAN = ceric ammonium nitrate, POPI = potassium phthalimide).



Figure 1. Synthesis of Ugi 4-CR and Passerini 3-CR adducts under mechanochemical activation (MM200 = Retsch Mixer Mill MM200). In continuation of our ongoing efforts to expand the applicability of HSBM activation in organic synthesis,^[5c,5d,5f,5l,8b] we report herein the liquid-assisted grinding (LAG) synthesis of Ugi 4-CR adducts and the solvent-free synthesis of Passerini 3-CR adducts, both under ball-milling conditions (Figure 1).

Results and Discussion

Ugi Reaction

We began this study by evaluating the feasibility of a solventfree Ugi 4-CR reaction. The synthesis of Ugi adduct **5a** was chosen as our model reaction, which employed *tert*-butyl isocyanide (1), benzaldehyde (2), chloroacetic acid (3), and propargylamine (4) as the starting materials with indium(III) chloride (2 mol-%) as the catalyst in a Retsch Mixer Mill MM200 ball mill under mechanochemical activation (Table 1).



Table 1. Screening of reaction conditions for the solvent-free Ugi four-component reaction. $^{\left[a\right] }$

	$ \begin{array}{c} \oplus\\ & & \\ &$	HSBM MM200, 25 Hz InCl₃ (2 mol-%)	→ E E	
Entry	Additive (mg)	Reactor type, ^[b]	Time [min]	Yield ^[c]
		no. balls (d [mm])	(cycles)	[%]
1	-	Met-A, 2 (6)	90 (1)	46
2	SiO ₂ (200)	Met-A, 2 (6)	90 (1)	57
3	SiO ₂ /NaHSO ₄ (200)	Met-A, 2 (6)	90 (1)	33
4	SiO ₂ (200)	Met-B, 2 (6)	90 (1)	63
5	SiO ₂ (200)	Met-B, 2 (6)	90 (2)	70
6	SiO ₂ (200)	Met-B, 2 (4)	90 (2)	34
7	SiO ₂ (200)	Met-B, 1 (6)	90 (2)	73
8	SiO ₂ (200)	Met-B, 1 (6)	90 (3)	71
9	SiO ₂ (150)	Met-B, 1 (6)	90 (2)	61
10	SiO ₂ (100)	Met-B, 1 (6)	90 (2)	59
11	SiO ₂ (50)	Met-B, 1 (6)	90 (2)	66
12	NaCl (200)	Met-B, 1 (6)	90 (2)	50
13	Al ₂ O ₃ -neutral (200)	Met-B, 1 (6)	90 (2)	32
14	Al ₂ O ₃ -basic (200)	Met-B, 1 (6)	90 (2)	33
15	Al ₂ O ₃ -acid (200)	Met-B, 1 (6)	90 (2)	60
16 ^[d]	CSA (200)	Met-B, 1 (6)	90 (2)	47
17 ^[e]	SiO ₂ (200)	agate, 1 (6)	90 (2)	55

[a] All reactions were carried out on a 0.5 mmol scale by using equimolar amounts of the reactants. [b] Reactor type: Met-A, stainless steel [diameter (d): 2.0 cm; height: 2.0 cm; volume of reactor: 10.5 mL]; Met-B, stainless steel (diameter: 1.2 cm; height: 2.0 cm; volume of reactor: 3.2 mL); agate (diameter: 1.2 cm; height = 2.0 cm; volume of reactor: 3.2 mL). [c] Yield of isolated products after purification by flash column chromatography. [d] CSA = cellulose-chlorosulfonic acid. [e] Reaction was carried out with one ball of agate (diameter: 6 mm).

The Met-A experiments examined the use of a stainless steel reactor (diameter: 2.0 cm; height: 2.0 cm; volume of reactor: 10.5 mL) that contained two balls of the same material (diameter: 6 mm; mass: 1.04 g) and a milling time of 90 min at 25 Hz. After purification by flash column chromatography, the anticipated Ugi adduct **5a** was isolated as a stable solid in 46 % yield (Table 1, Entry 1). The effect of the addition of solid supports such as SiO₂ (silica gel, 230–400 mesh) and silica-supported sodium hydrogen sulfate (SiO₂/NaHSO₄)^[24] was also examined. These experiments afforded Ugi adduct **5a** in 57 and 33 % yield, respectively (Table 1, Entries 2 and 3).

Encouraged by the beneficial effect of silica gel in the reaction medium, we carried out two additional experiments with the additive in a smaller stainless steel reactor [Met-B (diameter: 0.6 cm; height: 2.0 cm; volume of reactor: 3.2 mL)]. In these cases, the desired product was produced in 63 and 70 % yield after milling for 90 and 180 min, respectively, at 25 Hz, (Table 1, Entries 4 and 5). The use of smaller milling balls (diameter: 4 mm; mass: 0.43 g) was not convenient, as the yield of **5a** decreased to 34 % (Table 1, Entry 6). Decreasing the number of balls and/or increasing the grinding time to 270 min resulted in similar conversions (Table 1, compare Entries 7 and 8 relative



to Entry 5). Subsequently, the potential effect of the load of the additive (SiO₂) in the reaction was evaluated. A slight decrease in the yield of **5a** (59–66 %) occurred when lower amounts of SiO₂ were used (Table 1, Entries 9–11). Other additives such as NaCl,^[25] neutral Al₂O₃, basic Al₂O₃, acidic Al₂O₃, and CSA^[26] also afforded Ugi adduct **5a** in a low yield (32–60 %; Table 1, Entries 12–16). Finally, when the reaction was performed in an agate mill jar (one ball of agate; diameter: 6 mm; mass: 0.44 g), the reaction proceeded to give the product in 55 % yield (Table 1, Entry 17), which suggests that the process does not significantly depend on the material of the reactor.

Although the use of silica gel as a promoter in isocyanidebased multicomponent reactions has been reported,^[27] there are no previous reports of its use in the Ugi reaction under high-speed ball-milling conditions. The weak Brønsted acid nature of silica may be a plausible explanation for the positive effect of this additive in the reaction. In particular, the hydroxy groups of the silica gel skeleton may activate the formation of the initial imine intermediate through hydrogen bonding, which facilitates the formation of the corresponding Ugi adduct.

With regard to the use of silica gel as an additive, it is important to note that the physical state of the reactants plays a key role in the progress of the reaction. In our system, a brownish crude oil was obtained after initially combining the reagents, three of which are liquids [benzaldehyde (2), propargylamine (4), and tert-butyl isocyanide (1)] and two are solids [chloroacetic acid (3) and InCl₃]. The oily nature of the reaction mixture appears to favor its adsorption onto the surface of the silica. Interestingly, after the milling process, the crude product is afforded as a fine pale yellowish powder with an evident decrease in the particle size, as a consequence of the micropulverization process.^[28] Nevertheless, handling of the adsorbed mixture of the crude product and silica was difficult and prevented purification by flash column chromatography. Isolation of the pure product instead required an extraction process with 15 mL of CH₂Cl₂/MeOH (1:1) for a 0.5 mmol scale reaction. To avoid the extraction process, we decided against the use of silica gel for the solid-assisted grinding of the reaction.

Thus, a liquid-assisted grinding^[29] process was explored by employing the optimized reaction conditions (i.e., Table 1, Entry 7) but in the absence of the silica gel. Methanol was selected for such a strategy, as it is usually employed as the solvent for Ugi reactions. For comparison purposes, the reaction was initially conducted without the LAG, which afforded the Ugi adduct in 59 % yield (Table 2, Entry 1). The positive effect of LAG {50 µL of MeOH, $\eta = 0.29$ µL mg⁻¹ [η is the ratio of the amount of solvent employed (in µL) for LAG/the total mass of reagents (in mg)]]^[29a] was evident by the improved reaction performance after milling for 180 min (Table 2, Entry 2). Nevertheless, a reaction time of 45 min was sufficient for this system, as comparable conversions were obtained by milling for 90 and 180 min (Table 2, Entries 2-4). In this regard, a considerable increase in yield was observed with the use of 75 μ L (η = 0.44 μ L mg⁻¹) and 100 μ L (η = 0.59 μ L mg⁻¹) of methanol as the additive for the LAG (Table 2, Entries 5 and 6). On the other hand, a decrease in grinding time (Table 2, Entries 7 and 8), the





frequency (20 Hz, Table 2, Entry 9), or an increase in the number of milling balls (Table 2, Entry 10) had a deleterious effect.

Table 2. Screening of liquid-assisted grinding conditions for the Ugi reaction under $\mathsf{HSBM}^{[a]}_{}$



[a] All reactions were carried out on a 0.5 mmol scale by using equimolar amounts of reactants. [b] Yield of isolated products after purification by flash column chromatography. [c] Reaction carried out using a frequency of 20 Hz. [d] Reaction was carried out with two balls (diameter: 6 mm).

In summary, liquid-assisted grinding (75 μ L of MeOH, η = 0.44 μ L mg⁻¹) for the HSBM-activated Ugi reaction provided better overall results than those obtained by using silica gel as the solid additive (Table 2, Entry 5).

With the optimal conditions at hand (Table 2, Entry 5), the scope of the liquid-assisted grinding process for the Ugi multicomponent reaction under HSBM activation was examined. In particular, the influence of electron-withdrawing (4-Cl, 4-Br, 4-CF₃, and 4-NO₂) and electron-donating substituents [4-OMe, 4-CH₃, and 4-N(CH₃)₂] on the benzaldehyde was examined (Table 3).

In the case of electron-withdrawing groups, good yields (53-73 %) of Ugi adducts 5b-5e were obtained with grinding times of 90-180 min (Table 3). Similarly, the use of benzaldehyde derivatives that contained electron-donating groups afforded the corresponding adducts 5f-5i in moderate to good yields (46-65 %) after isolation by column chromatography (Table 3). Additionally, the synthesis of Ugi adducts 5j-5m derived from polyaromatic (biphenyl-4-carbaldehyde and 1-naphthaldehyde), heteroaromatic (pyrrole-2-carbaldehyde), and aliphatic (cyclohexanecarbaldehyde) aldehydes led to the formation of the expected products in good yields (52-69 %; Table 3). The use of alternative reagents such as cyclohexyl isocyanide, benzylamine, and benzoic acid as substitutes for tert-butyl isocyanide (1), propargylamine (4), and chloroacetic acid (3), respectively, afforded adducts 5n-5p in 48-56 % yield, which extended the scope of the HSBM process (Table 3). For the synthesis of 5e, 5h, and 5l, using an agate mill jar (one ball of agate; diameter: 6 mm) was convenient to prevent the decomposition of the

Table 3. Scope of the present method.^[a,b]



[a] All reactions were carried out on a 0.5 mmol scale by using equimolar amounts of reactants. [b] Yields are reported for isolated products after purification by flash column chromatography. [c] Reaction was carried out in an agate mill jar using one ball of agate (diameter: 6 mm). [d] Yield of Ugi adduct previously reported by El Kaïm et al.^[30d] [e] MeOH (0.33 M), InCl₃ (2 mol-%), microwave (MW), 50 °C, 2 h. [f] Yield of Ugi adduct previously reported by Bahulayan et al.^[30e] [g] Yield of Ugi adduct previously reported by Miranda et al.^[30a]

desired adducts, which was observed when the reactions were carried out in a stainless steel reactor (Table 3).

To compare the efficiency of the solvent-free protocol developed here with that of solvent-based methods, the synthesis of **5I** was carried out under previously reported solution conditions [MeOH (0.33 M), $InCl_3$ (2 mol-%), MW, 50 °C, 2 h].^[30a] Adduct **5I** was obtained in 29 % yield (Table 3), which is a significantly lower conversion value than that obtained by the milling process. This result can be attributed to the partial decomposition of the pyrrole-2-carbaldehyde in solution, a behavior that





is prevented under mechanochemical conditions (agate reactor). For comparison purposes, the yields of Ugi adducts **5f**,^[30d] **5o**^[30e] and **5p**,^[30a] which were previously obtained under solution conditions, are included in Table 3. The details provided show the advantages of the HSBM process in terms of the minimization of solvent use and the reduction of reaction times (Table 3; compounds **5f** and **5o**).

Passerini 3-CR Reaction

Encouraged by the results of the Ugi reaction under HSBM activation, we envisioned the possibility of applying this activation mode to the Passerini reaction. This multicomponent reaction has been widely employed in organic synthesis but never under solvent-free mechanochemical activation. Thus, we considered it important to explore the feasibility of carrying out the Passerini reaction under solvent-free conditions.

The study of the Passerini reaction was initially performed with benzoic acid (**6**), benzaldehyde (**2**) and *tert*-butyl isocyanide (**1**) as the model reagents under the optimized mechanochemical conditions that were previously established for the Ugi reaction [frequency: 25 Hz; grinding time: 90 min; stainless steel reactor (Met-B); one stainless steel ball (diameter: 6 mm)]. The results are summarized in Table 4. After purification by flash column chromatography, Passerini adduct **7a** was obtained as a white solid in 65 % yield (Table 4, Entry 1).

Table 4. Screening of reaction conditions for solvent-free Passerini MCR.^[a]



[a] All reactions were carried out on a 0.5 mmol scale by using equimolar amounts of reactants. [b] Yield of isolated products after purification by flash column chromatography. [c] Yield after basic workup with NaOH (0.1 \aleph). [d] Reaction was carried out with two balls (diameter: 6 mm). [e] Isocyanide (1.2 equiv.) was employed.

In subsequent experiments, the potential influence of the milling time was evaluated. Reactions with 120 and 180 min of milling time afforded yields comparable with that of 90 min of milling time (Table 4, Entries 2 and 3). Nevertheless, a considerable decrease in the yield was observed with 30 and 60 min of grinding time (Table 4, Entries 4 and 5). Interestingly, employing the conditions described in Table 4, Entry 1 but with two stain-

less steel balls, instead of one, afforded adduct **7a** in 73 % yield (Table 4, Entry 6). In contrast, the use of small amounts of MeOH (75 μ L, $\eta = 0.44 \ \mu$ L mg⁻¹ and 100 μ L, $\eta = 0.59 \ \mu$ L mg⁻¹) and the liquid-assisted grinding strategy resulted in lower yields of Passerini adduct **7a** (Table 4, Entries 7–9).

With the optimized conditions at hand, we explored the scope of the method by using different substituted aromatic aldehydes such as those that contain the electron-withdrawing groups 4-Cl, 4-CF₃, and 4-NO₂. The corresponding Passerini adducts **7b**–**7d** were produced in good to excellent yields (67–92%) after basic workup (Table 5). Benzaldehydes with electron-donating groups such as 4-OCH₃ and 4-CH₃ were also studied and found to furnish products **7e** and **7f** in moderate to good yields (43–52%). These results show that there is a clear electronic effect on the reaction. Additionally, polyaromatic aldehydes such as biphenyl-4-carbaldehyde and 1-naphthaldehyde generated the anticipated products **7g** and **7h** in good to excellent yields (64–84%) without the need for purification by column chromatography (Table 5). However, benzoic acids that contain electron-withdrawing groups such as 4-NO₂

Table 5. Scope of the solvent-free Passerini methodology.^[a,b]



[a] All reactions were carried out on a 0.5 mmol scale. [b] Yield of isolated products are provided after workup with NaOH (0.1 $_{N}$). [c] Purification by flash column chromatography. [d] Grinding time: 180 min.





and 4-Cl afforded the desired Passerini adducts **7i** and **7j** in acceptable yields (42 %). Finally, the use of aliphatic acids and other isocyanides such as 3-bromopropionic acid and cyclohexyl isocyanide generated the corresponding adducts **7k** and **7l** in 46 and 85 % yield, respectively (Table 5).

To compare reactions conditions and results, those Passerini adducts (i.e., **7a**,^[20c,31] **7b**,^[20c,31a,32] **7f**,^[31a,31c,31d] and **7l**^[31b,33]) that were obtained under HSBM conditions as well as by other previously reported methods are presented in Table 6.

Table 6. Yields of Passerini products obtained under HSBM conditions and by previously reported methods.

Adduct	HSBM yield [%]	Literature yield [%]; conditions	Ref.
7a	73	94; DMSO, ^[a] NaHCO ₃ , 90 °C, 5 h	[31a]
7a		83; flow chemistry	[31b]
7a		88; solvent-free, 180 °C, 4 min	[20c]
7a		88; [bmim][BF ₄], ^[a] 60 °C, 9 h	[31c]
7a		82; [bmim][BF ₄]), 60 °C, 9 h	[31d]
7b	67	96; DMSO, NaHCO ₃ , 90 °C, 5 h	[31a]
7b		86; solvent-free, 180 °C, 4 min	[20c]
7b		88; MW, 120 °C, 1.0 min	[32a]
7b		55; PS- <i>p</i> TsOH, ^[a] room temp., 48 h	[32b]
7f	52	94; DMSO, NaHCO ₃ , 90 °C, 5 h	[31a]
7f		72; [bmim][BF ₄], 60 °C, 7 h	[31c]
7f		62; [bmim][BF ₄], 60 °C, 7 h	[31d]
71	85	86; flow chemistry	[31b]
71		85; H ₂ O, Me ₃ SiN ₃ , PhMe, reflux	[33a]
71		74; O ₂ , TEMPO, ^[a] tBuONO, room temp., 24 h	[33b]

[a] DMSO = dimethyl sulfoxide; bmim = 1-butyl-3-methylimidazolium; PSpTsOH = polymer-supported p-toluenesulfonic acid; TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

The yields are comparable in most cases, but it is important to note that the use of the solvent-free mechanochemistry presents advantages in terms of the minimization of solvent use, the lower-energy consumption, shorter reaction times, and simpler reaction conditions (Table 6).

To demonstrate the synthetic utility of the present HSBM protocols, both the Ugi and Passerini processes were scaled up to 4 mmol, which afforded Ugi adduct **5a** and Passerini adduct **7a** in 55 (0.694 g) and 75 % yield (0.930 g), respectively

(Scheme 2; for experimental details, see Supporting Information). In the Ugi reaction, a crude dark brown oily product was obtained after milling, with an apparent change in color and consistency compared with the initial reaction mixture (pale brown). In contrast, a gray solid was obtained as the crude product of the Passerini reaction, with a noticeable change in the physical states of the reactants (liquid) versus the product (solid).



Scheme 2. Large-scale synthesis of the Ugi and Passerini adducts 5a and 7a.

Synthesis of Xanthate-Based Radical Precursors under Ball-Milling Conditions

With a goal to carry out a synthetic modification of the Ugi adducts by using mechanochemically activated multicomponent reactions, we subjected **5a**, **5b**, and **5e** to an additional transformation under HSBM activation (Scheme 3). The synthesis of the xanthate-based radical precursors **9a**–**9c**^[34] was achieved by a nucleophilic $S_N 2$ substitution reaction using potassium ethyl xanthogenate (**8**) and 90 min of milling at



Scheme 3. Synthetic transformations of Ugi adducts 5a, 5b, and 5c by using mechanochemical activation.





25 Hz under solvent-free conditions to afford the xanthates in 71–89 % yield (Scheme 3). To the best of our knowledge, the synthesis of radical precursors **9a–9c** is the first example of a mechanochemically activated xanthate synthesis.

Conclusions

A practical synthesis of Ugi 4-CR adducts (5a-5p, 46-74% yield) and Passerini 3-CR adducts (7a-7l, 40-92 % yield) under ball-milling conditions was developed to demonstrate the usefulness of mechanochemical activation for isocyanide-based multicomponent reactions. These protocols allow for the preparation of valuable molecules in moderate to good yields by using green chemistry principles, that is, by using environmentally friendly processes that require no purification steps (Passerini reaction) and form a nontoxic (H₂O) byproduct. Furthermore, these MCRs have high atom economy, simple reaction conditions, short reaction times, and low energy costs. Additionally, it was shown that other useful organic transformations can be carried out under solvent-free mechanochemical activation, such as the synthesis of valuable xanthates. Finally, both the Ugi and Passerini processes could be scaled up to 4 mmol. We believe that these results will have a positive impact on the fields of mechanochemistry and multicomponent reactions.

Experimental Section

General Methods: Mechanochemical experiments were carried out in a Retsch MM200 ball mill that was equipped with one of three possible types of reactors. The Met-A (diameter: 2.0 cm; height: 2.0 cm; volume of reactor: 10.5 mL) or the Met-B (diameter: 1.2 cm; height: 2.0 cm; volume of reactor: 3.2 mL) stainless steel jar equipped with stainless steel balls (diameter: 6 mm; mass: 1.04 g; diameter: 4 mm; mass: 0.43 g; diameter: 11.0 mm; mass: 6.89 g) was employed. Alternatively, an agate mill jar (diameter: 1.2 cm; height: 2.0 cm; volume of reactor: 3.16 mL) equipped with one ball of agate (diameter: 6 mm; mass: 0.44 g) was employed. All reagents and solvents were obtained from Sigma-Aldrich and used without further purification. Flash column chromatography (FCC) was performed with Macherey-Nagel silica gel 60 S2 (230-400 mesh). The NMR spectroscopic data were recorded with Jeol ECA (500 MHz), Jeol Eclipse (400 MHz), and Bruker DP300 (300 MHz) spectrometers. The ¹H NMR chemical shifts and coupling constants were determined by assuming first-order behavior. The multiplicities of the NMR signals are reported by using the following abbreviations: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). The microwave-assisted reactions were performed by using a CEM Discover SynthesisTM unit (CEM corp., Matthews, NC) with a monomodal open-vessel system. Melting points were measured with a Büchi B-540 instrument. High-resolution mass spectra were recorded with an LC/MSD-TOF Agilent mass spectrometer. IR spectra were measured with a Perkin-Elmer (PC16, Spectrum GX) FTIR/FIR spectrometer with attenuated total reflectance (ATR). Elemental analyses were performed with a Thermofinigann Flash 1112 apparatus.

General Procedure for the Mechanochemical Synthesis of Ugi Adducts (5a–5p): A mixture of the benzaldehyde (0.5 mmol, 1.0 equiv.), carboxylic acid (1.0 equiv.), amine (1.0 equiv.), and iso-cyanide (1.0 equiv.) along with $InCl_3$ (2 mol-%) and MeOH (75 µL)

was milled in a stainless steel grinding vial (diameter: 1.2 cm; height: 2.0 cm; volume of reactor: 3.2 mL) equipped with a stainless steel ball (diameter: 6 mm; mass: 1.04 g) for 45 min at 25 Hz. The resulting crude product mixture was transferred with CH_2CI_2 (2.0 mL) for purification by flash column chromatography (SiO₂).

Supporting Information (see footnote on the first page of this article): Experimental details and spectroscopic data.

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